Received: 22 February 2022 | Revised: 13 July 2022 | Accepted: 20 July 2022 | Published online: 25 August 2022

DOI: 10.1002/dad2.12351

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Associations of the Lifestyle for Brain Health index with longitudinal cognition and brain amyloid beta in clinically unimpaired older adults: Findings from the Wisconsin Registry for Alzheimer's Prevention

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Abstract

Introduction: Modifiable health and lifestyle factors increase risk of dementia, but whether modifiable factors, when measured in late-midlife, impact the emergence or progression of Alzheimer's disease (AD) pathophysiologic or cognitive changes remains unresolved.

Methods: In initially cognitively unimpaired, late middle-aged participants ($N = 1215$; baseline age, M [standard deviation] = 59.3 [6.7] years) from the Wisconsin Registry for Alzheimer's Prevention (WRAP), we investigated the influence of the Lifestyle for Brain Health (LIBRA) index, a lifestyle-based dementia risk score, on AD-related cognitive trajectories and amyloid beta (Aβ) plaque accumulation.

Results: Overall, lower baseline LIBRA, denoting healthier lifestyle and lower dementia risk, was related to better overall cognitive performance, but did not moderate apolipoprotein E ε4 or Aβ-related longitudinal cognitive trajectories. LIBRA was not significantly associated with Aβ accumulation or estimated age of Aβ onset.

Discussion: In WRAP, late-midlife LIBRA scores were related to overall cognitive performance, but not AD-related cognitive decline or Aβ accumulation in the preclinical timeframe.

KEYWORDS
amyloid, apolipoprotein E ε4, biomarkers, cognitive impairment, lifestyle, positron emission tomography, preclinical Alzheimer's disease, risk factors

Funding information
NIH, Grant/Award Numbers: R01AG027161, RO1AG021155; AARF, Grant/Award Number: 19614533; NICHD, Grant/Award Numbers: P50HD105353, S10 OD025245-01; the University of Wisconsin Institute for Clinical and Translational Research NIH, Grant/Award Number: UL1TR002375

Highlights

- The Lifestyle for Brain Health (LIBRA) index was associated with cognitive performance in late-midlife.
- LIBRA did not moderate apolipoprotein E ε4 or amyloid-related cognitive decline.
- LIBRA was not associated with the onset or accumulation of amyloid plaques.

1 | BACKGROUND

The pathophysiological progression of Alzheimer's disease (AD) begins with amyloid beta (Aβ) plaque accumulation and can occur two or more decades before clinical symptom onset.[1–6] Characterizing this preclinical or pre-symptomatic phase is critical for the development of effective intervention or preventive strategies. With the long prodromal period and current lack of effective treatments, attention has shifted toward preventive strategies focusing on modifiable factors that may prevent or delay the onset of dementia.[7–10] The availability of neuroimaging and fluid AD biomarkers now provides opportunity to study associations between modifiable risk factors and AD pathophysiologic and cognitive changes in the decades preceding dementia, before irreparable brain damage and cognitive symptoms occur.

Longitudinal observational studies of preclinical AD have demonstrated that cognitively unimpaired individuals with elevated Aβ exhibit faster cognitive decline and are at an increased risk for clinical disease progression;[11–14] further, recent evidence indicates that the duration of amyloid exposure in these individuals is associated with more rapid cognitive decline and increased tau burden.[6] It remains unclear whether modifiable lifestyle factors, when measured in combination, impact the emergence or progression of AD pathophysiologic or cognitive changes. Understanding the associations between modifiable lifestyle factors and longitudinal cognition in the preclinical phase of AD is critical, as modifiable factors constitute potential targets for therapeutics and preventive strategies.

The common co-occurrence of modifiable health and lifestyle factors of dementia and the increasing focus on early intervention have stimulated the development of dementia risk scores, like the Lifestyle for Brain Health (LIBRA) index, which was developed based on a systematic literature review and Delphi consensus.[8] It is a compound score, comprised of 12 modifiable lifestyle factors that are amenable to change and thus reflects one's prevention potential for dementia.[8] Several population- and patient-based cohort studies have demonstrated that lower LIBRA scores, denoting healthier lifestyle and lower lifestyle-based dementia risk, are associated with better cognitive functioning and lower risk of mild cognitive impairment (MCI) and dementia in mid- and late-life.[15–19] Whether modifiable lifestyle factors, as indexed by the LIBRA score, interact with genetic risk (e.g., apolipoprotein E [*APOE*] ε4 genotype) or Aβ burden on preclinical cognitive decline in the context of AD remains to be elucidated.

Therefore, in the present study, we examined whether LIBRA, a well-validated multivariable measure of modifiable lifestyle-based dementia risk, moderates *APOE* ε4 or Aβ-related longitudinal cognitive decline among late middle-aged, initially unimpaired individuals from the Wisconsin Registry for Alzheimer's Prevention (WRAP). Additionally, we examined whether LIBRA in late-midlife is associated with Aβ accumulation or estimated age of Aβ onset.

2 | METHODS

2.1 | Participants

Data were from individuals enrolled in WRAP, an ongoing longitudinal observational study that follows a cohort of >1500 asymptomatic (at study entry), late-middle aged adults.[20] The WRAP sample is enriched for family history of AD, with >70% of WRAP participants having a parent with either autopsy-confirmed or probable AD as defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association research criteria.[20,21] The overarching goal of WRAP is to characterize the emergence and progression of AD from late-midlife into old age. Participation in WRAP includes biennial evaluations that involve a physical and health examination, neuropsychological assessment, and optional linked studies for acquisition of neuroimaging or fluid biomarkers of AD pathophysiology. At each study visit, WRAP participants were clinically diagnosed based on National Institute on Aging–Alzheimer's Association workgroup diagnostic criteria, confirmed through a multi-disciplinary consensus diagnosis panel.[22] Briefly, diagnoses included cognitively unimpaired, MCI, impaired—not MCI, and dementia. WRAP participants with complete LIBRA (described below), genetic, and cognitive data who were cognitively unimpaired at baseline (defined as their first visit with complete LIBRA factor data) were included in the current study ($n = 1215$; see Figure S1 in supporting information for detailed inclusion/exclusion criteria). *APOE* ε4 was genotyped as previously described.[23] Participants were categorized as *APOE* ε4 carriers (one or two ε4 alleles) or noncarriers (zero ε4 alleles). All subjects provided informed consent and study procedures were approved by the University of Wisconsin–Madison Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

2.2 | Cognition

WRAP participants completed cognitive assessments at their initial study visit and approximately every 2 years thereafter. Longitudinal

RESEARCH IN CONTEXT

1. **Systematic Reviews**: The authors reviewed the literature using traditional databases (e.g., PubMed). Few studies have been published using the same lifestyle and health-based dementia risk score, the Lifestyle for Brain Health (LIBRA) index. However, this study is the first to examine LIBRA in relation to preclinical Alzheimer's disease (AD) pathophysiologic and cognitive changes.
2. **Interpretation**: In our late-middle aged, initially unimpaired sample, baseline LIBRA was associated with overall cognitive performance when accounting for the negative influence of apolipoprotein E (*APOE*) ε4 and amyloid beta (Aβ) on cognitive decline. There was no evidence that LIBRA was related to Aβ accumulation or moderated *APOE* ε4 or Aβ-related cognitive decline in the pre-symptomatic timeframe.
3. **Future Directions**: Lifestyle, as indexed by LIBRA, may not be related to the emergence or progression of AD in the early, preclinical stages of the AD continuum; whether lifestyle is related to pathophysiologic or cognitive changes in later AD stages deserves further study.

cognitive performance was assessed using the Preclinical Alzheimer's Cognitive Composite (PACC-3), a cognitive composite that has been shown to be sensitive to preclinical Aβ burden.[6,13,14,24] The WRAP PACC-3[25] is derived from the Rey Auditory Verbal Learning Test total learning score (RAVLT; Trials 1–5), Wechsler Memory Scale–Revised Logical Memory delayed recall score,[26] and the Wechsler Adult Intelligence Scale–Revised Digit Symbol test score.[27]

2.3 | Operationalization of the LIBRA score

LIBRA is a weighted sum score (theoretical range = −5.9 to +12.7; with lower scores indicating healthier lifestyle and lower lifestyle-based dementia risk) comprised of 12 modifiable factors that can be targeted by lifestyle interventions and primary prevention. Risk factors include physical inactivity, smoking, depression, hypertension, obesity, diabetes, hypercholesterolemia, coronary artery disease, and renal disease. Protective factors include low-to-moderate alcohol use, high cognitive activity, and healthy diet. In WRAP, longitudinal data on diet was lacking and thus was not included in the overall risk score. The individual LIBRA factors were created based on clinical data from physical examination or self-reported questions and then dichotomized based on previously established cut-offs (Table 1). The LIBRA total score was calculated from the 11 available factors in WRAP using a previously reported approach, in which a weight (positive for presence of risk factors; negative for presence of protective factors; Table 1) was assigned to each factor in accordance with the relative risks from published meta-analyses.[8,18,28] Table 1 provides an overview of available LIBRA factors, assigned weights, and operationalization in this dataset.

2.4 | Positron emission tomography imaging

A subset of participants (N = 285) underwent T1-weighted magnetic resonance imaging (MRI; 3T GE Signa 750) as well as Aβ (^{11}C-Pittsburgh compound B [PiB]) positron emission tomography (PET) imaging. Detailed methods for radioligand synthesis and PET and MRI acquisition, processing and quantification, and analysis were implemented as reported previously.[29,30] Aβ burden was assessed as a global cortical average PiB distribution volume ratio (DVR),[29] and a previously established threshold of DVR >1.19 was used to determine Aβ positivity.[31] Age of Aβ onset and Aβ duration (age at visit − estimated age Aβ+), defined as the approximate number of years that an individual has had suprathreshold Aβ positivity, were estimated using a combination of group-based trajectory modeling and Bayes' theorem.[6]

2.5 | Statistical analyses

Statistical analyses were performed with R version 4.0.5 (The R Foundation). Kruskal–Wallis and chi-squared tests were used to examine baseline differences in demographics and LIBRA factors among three LIBRA risk groups based on LIBRA tertiles (low risk: LIBRA scores between −4.2 and 0; moderate risk: LIBRA scores between 0.1 and 2.0; High risk: LIBRA scores between 2.1 and 8.1; Table 2).

To examine whether baseline LIBRA moderates the negative associations of *APOE* ε4 or Aβ duration with cognitive decline, we modeled longitudinal standardized PACC-3 trajectories using linear mixed effects (LME) models (*nlme* package, R). Models included age, age^2, sex, baseline Wide Range Achievement Test 3rd Edition (WRAT3) reading score, and practice fixed effects (age and WRAT3 centered using baseline means) as well as subject-specific random intercepts and age-related slopes (unstructured covariance).[6] The first set of LME models (N = 1215) included a three-way interaction among baseline LIBRA, *APOE* ε4 carriage, and age to determine whether lifestyle and genetic risk increase the likelihood of cognitive decline beyond their separate effects (i.e., synergistic effect). A second set of LME models (PiB subset, N = 285) examined the combined influence of baseline LIBRA and Aβ duration on longitudinal PACC-3, and included a three-way interaction among baseline LIBRA, Aβ duration, and age. For each set, we followed a backward stepwise approach, removing highest order non-significant interactions sequentially. Two-sided P-values <.05 were considered statistically significant, and Akaike information criteria (AIC) statistics were used to determine the model of best fit. Secondary analyses repeated each LME model set using time-varying LIBRA (i.e., LIBRA at each cognitive assessment) to assess whether concurrent LIBRA moderates the negative associations of *APOE* ε4 carriage or Aβ duration on PACC-3 decline.

Associations of baseline LIBRA with Aβ burden and estimated age of Aβ onset were investigated using linear regressions that

TABLE 1 Operationalization of LIBRA factors

Modifiable factor	Definition	Weight[a]
Low/moderate alcohol use	Self-reported frequency of alcohol use, where low-to-moderate consumption was defined as two drinks or less in a day for men and one drink or less per day for women, including (non-drinkers).	−1.0
Coronary artery disease	Coronary artery disease was based on physician review of self-reported medical history. Coronary artery disease included history of recurrent chest pain with exercise (angina pectoris), history of heart attack (myocardial infarction), or history of cardiac interventions (e.g., angioplasty, stenting, or coronary bypass surgery).	+1.0
Physical inactivity	Self-reported physical activity on CHAMPS questionnaire, where physical inactivity was defined as fewer than 150 minutes of moderate exercise per week.	+1.1
Renal dysfunction	The Chronic Kidney Disease Epidemiology Collaboration equation was used to estimate GFR from serum creatinine and other clinical parameters, and renal dysfunction was defined as GFR < 60 mL/min/1.73m^2.	+1.1
Diabetes	Diabetes was determined from self-reported use of anti-diabetic medication or, if no self-report, fasting blood glucose ≥126 mg/dL.	+1.3
High cholesterol	Hypercholesterolemia was defined as self-reported use of anti-cholinergic medication or, if no self-report, total serum cholesterol ≥240 mg/dL.	+1.4
Smoking	Smoking was defined from self-reported history of smoking at least once in the past month.	+1.5
Obesity	BMI ≥30 kg/m^2 calculated from physical examination at the study visit.	+1.6
Hypertension	Hypertension was defined as self-report of use of anti-hypertensive medication or, if no self-report, mean systolic blood pressure ≥130 mmHg or mean diastolic blood pressure ≥80 mmHg.	+1.6
Depression	The Center for Epidemiologic Studies-Depression Scale was used to measure depressive symptoms. Participants were considered depressed if their sum score ≥16.	+2.1
High cognitive activity	Games score >4, on the Cognitive Activity Scale.	−3.2

Abbreviations: BMI, body mass index; CHAMPS, Community Healthy Activities Model Program for Seniors; GFR, glomerular filtration rate; LIBRA, Lifestyle for Brain Health index.

[a]LIBRA score, composed of available factors in the Wisconsin Registry for Alzheimer's Prevention (excluding Mediterranean diet, for which data was not available). Positive weights are assigned to risk factors, and negative weights are assigned to protective factors. Total range −5.9 to 12.7; range adjusted to this study −4.2 to 12.7

covaried age at PiB PET visit, *APOE* ε4, and time between baseline LIBRA and PiB visit ($N = 285$). In the subset with two or more PiB scans ($N = 178$), we ran similar models using annualized PiB DVR change to examine whether baseline LIBRA was associated with Aβ accumulation rate.

3 | RESULTS

3.1 | Participants

Baseline sample characteristics and frequency of LIBRA factors are presented overall and by baseline LIBRA risk groups (Table 2). Over a median (interquartile range [IQR]) of 6.9 (3.4–9.3) years of cognitive follow-up, 1181 (97.2%) participants remained unimpaired and 31 (2.6%) participants progressed to MCI or dementia. Individuals in the high LIBRA risk group, had fewer years of education and worse WRAT3 performance compared to individuals in the low LIBRA risk group. The proportion of LIBRA risk factors increased stepwise across LIBRA risk groups (e.g., low risk < moderate risk < high risk). Physical inactivity, diabetes, high cholesterol, smoking, obesity, hypertension, and depression were more common risk factors in the high LIBRA risk group, and high cognitive activity was a more common protective LIBRA factor in the low LIBRA risk group. No differences in PiB PET measures of Aβ were observed across LIBRA risk groups (Table 2).

3.2 | LIBRA and longitudinal cognitive decline

Of primary interest was whether baseline LIBRA moderates the negative association of *APOE* ε4 or Aβ-related longitudinal decline. In the LME models ($N = 1215$, up to six cognitive assessments per participant) investigating late-midlife longitudinal PACC-3, the baseline LIBRA × *APOE* ε4 carriage × age interaction provided no statistical evidence that baseline lifestyle attenuates *APOE* ε4-related cognitive decline (LIBRA × *APOE* ε4 carriage × age^2, $P = .18$; LIBRA × *APOE* ε4 carriage × age, $P = .76$; Table S1 in supporting information). In the final reduced model (Table 3, Figure 1A), lower (i.e., healthier) baseline LIBRA was associated with better average PACC-3 performance ($P < .001$) and both the age and age^2 interactions with *APOE* ε4 carriage indicated significantly faster PACC-3 decline among *APOE* ε4 carriers. The parallel LME models in the PiB subset ($N = 285$, up to five cognitive assessments per participant) examining the interactive associations of baseline LIBRA and baseline Aβ duration on longitudinal PACC-3 did not reveal a

TABLE 2 Sample characteristics: Overall and by LIBRA risk groups

Characteristics	Total sample (*N* = 1215)	Baseline LIBRA risk groups[a] 1. Low risk (*N* = 394)	2. Moderate risk (*N* = 429)	3. High risk (*N* = 392)	Group *P*-value[b]	Pairwise differences[b]
Age at LIBRA baseline	59.3 (6.7)	59.6 (7.0)	59.4 (6.6)	58.8 (6.6)	.38	–
No. of study visits, Median [range]	4 [1 to 6]	4 [1 to 6]	4 [1 to 6]	4 [1 to 6]	.17	–
Years of cognitive follow-up	6.4 (3.5)	6.6 (3.4)	6.4 (3.5)	6.2 (3.5)	.16	–
Clinical diagnosis at most recent visit						
Unimpaired	1181 (97.2%)	388 (98.4%)	415 (96.7%)	378 (96.4%)	.50	–
Mild cognitive impairment	27 (2.2%)	5 (1.3%)	12 (2.8%)	10 (2.6%)		–
Dementia	4 (0.3%)	1 (0.3%)	1 (0.2%)	2 (0.5%)		–
Impaired, other	3 (0.2%)	0 (0%)	1 (0.2%)	2 (0.5%)		–
APOE ε4 carriers	469 (38.6%)	143 (36%)	168 (39%)	158 (40%)	.49	–
Parental family history of AD[c]	924 (76%)	291 (74%)	327 (76%)	306 (78%)	.38	–
Female	853 (70.2%)	295 (75%)	290 (68%)	268 (68%)	.05	–
WRAT3 reading score	105.8 (9.5)	107.3 (9.0)	106.5 (9.0)	103.5 (10.1)	<.001	3 vs. 1,2
Years of education	15.8 (2.3)	16.2 (2.2)	15.9 (2.2)	15.3 (2.2)	<.001	All pairs
Baseline LIBRA factors[d]						
Low/moderate alcohol consumption	1037 (85.3%)	352 (89%)	387 (90%)	298 (76%)	<.001	2 vs. 3
Cardiovascular disease	28 (2.3%)	5 (1.3%)	10 (2.3%)	13 (3.3%)	.16	–
Physical inactivity	400 (32.9%)	47 (12%)	158 (37%)	195 (50%)	<.001	1 vs. 2,3
Renal dysfunction	88 (7.2%)	21 (5.3%)	29 (6.8%)	38 (9.7%)	.06	–
Diabetes	88 (7.2%)	6 (1.5%)	29 (6.8%)	53 (14%)	<.001	All pairs
High cholesterol	193 (15.9%)	38 (9.6%)	60 (14%)	95 (24%)	<.001	3 vs. 1,2
Smoking	74 (6.1%)	6 (1.5%)	16 (3.7%)	52 (13%)	<.001	3 vs. 1,2
Obesity	440 (36.2%)	51 (13%)	115 (27%)	274 (70%)	<.001	All pairs
Hypertension	648 (53.3%)	93 (24%)	234 (55%)	321 (82%)	<.001	All pairs
Depression	146 (12.0%)	14 (3.6%)	25 (5.8%)	107 (27%)	<.001	3 vs. 1,2
High cognitive activity	271 (22.3%)	198 (50%)	57 (13%)	16 (4.1%)	<.001	All pairs
Baseline LIBRA score	0.9 (2.2)	−1.5 (1.1)	0.9 (0.6)	3.4 (1.2)	<.001	All pairs
PiB PET subset	285 (23.5%)	96 (33.7%)	115 (40.4%)	74 (25.9%)	.10	–
Age at most recent Aβ PiB PET	67.1 (6.6)	67.9 (6.6)	67.0 (6.4)	66.2 (6.9)	.29	–
Global PiB DVR	1.15 (0.20)	1.18 (0.23)	1.15 (0.20)	1.13 (0.17)	.55	–
Aβ positive at most recent PiB visit[e]	67 (24%)	27 (28%)	26 (23%)	14 (18.9%)	.36	–
Participants with >1 PiB PET visits	178 (62%)	64 (66%)	65 (57%)	49 (66%)	.68	–
Years of PiB PET follow-up[f]	6.4 (2.3)	6.7 (2.1)	6.6 (2.1)	5.8 (2.5)	.45	–
Annualized change in global PiB DVR[f]	0.006 (0.015)	0.008 (0.017)	0.003 (0.013)	0.006 (0.015)	.35	–

Note: Values are present as Mean (SD) or No. (%) unless otherwise indicated.

Abbreviation: Aβ, amyloid beta; AD, Alzheimer's disease; *APOE*, apolipoprotein E; DVR, distribution volume ratio; LIBRA, Lifestyle for Brain Health index; PiB, Pittsburgh compound B; PET, positron emission tomography; WRAT3, Wide Range Achievement Test (3rd edition).

[a]LIBRA risk groups were determined using baseline LIBRA tertiles: low risk was defined as LIBRA scores between −4.2 and 0, moderate risk was defined as LIBRA scores between 0.1 and 2.0, high risk was defined as LIBRA scores between 2.1 and 8.1.

[b]Statistical tests: χ^2 or Fisher exact test for categorical variables, Kruskal–Wallis rank sum test for continuous variables; *P*-value for difference between Baseline LIBRA risk groups. For group tests with $P < .05$, unadjusted pairwise post hoc differences are reported.

[c]Four participants were missing information on parental family history of AD.

[d]See Table 1 for the details on the operationalization of LIBRA factors.

[e]Aβ positivity was defined as global PiB DVR > 1.19.

[f]Values shown for subset (*N* = 178) with longitudinal (>1) PiB PET visits.

TABLE 3 Associations of baseline LIBRA, *APOE* ε4, and baseline Aβ duration with longitudinal cognition

Covariate	β Estimate (95% CI)	*P*-value
Model A: Baseline LIBRA and *APOE* ε4 ($N = 1215$, up to six cognitive assessments per person)		
(Intercept)	0.0210 (−0.0370–0.0790)	.48
APOE ε4 carrier × Age^2	−0.0010 (−0.0015 to −0.0004)	<.001
APOE ε4 carrier × Age	−0.0081 (−0.0148 to −0.0014)	.02
APOE ε4 carrier	−0.0592 (−0.1293–0.0110)	.10
Baseline LIBRA	−0.0402 (−0.0554 to −0.0251)	<.001
Age^2	−0.0006 (−0.0009 to −0.0003)	<.001
Age	−0.0428 (−0.0488 to −0.0368)	<.001
Female	0.4482 (0.3755–0.5210)	<.001
WRAT3	0.0286 (0.0249–0.0322)	<.001
Practice	0.0902 (0.0749–0.1054)	<.001
Model B: Baseline LIBRA and Aβ duration ($N = 285$, up to five cognitive assessments per person)		
(Intercept)	0.1279 (-0.0225–0.2783)	.10
Baseline Aβ duration × Age^2	−0.0001 (−0.0001 to -0.0001)	<.001
Baseline Aβ duration × Age	−0.0008 (−0.0014 to −0.0002)	.006
Baseline Aβ duration	0.0041 (−0.0016–0.0098)	.15
Baseline LIBRA	−0.0477 (−0.0810 to −0.0143)	.005
Age^2	−0.0025 (−0.0036 to −0.0015)	<.001
Age	−0.0646 (−0.0832 to −0.0460)	<.001
Female	0.4019 (0.2568–0.5469)	<.001
WRAT3	0.0255 (0.0179–0.0331)	<.001
Practice	0.1066 (0.0748–0.1385)	<.001

Note: Estimates and 95% CIs are from the best fitting linear mixed effects models of: (Model A) baseline LIBRA, *APOE*ε4 carriage, and PACC-3 decline, and (Model B) baseline LIBRA, baseline Aβ duration, and PACC-3 decline. Models were reduced using a backward removal approach of non-significant terms (see Tables S1–S2 in supporting information). Age and WRAT3 were mean centered.

Abbreviation: Aβ, amyloid beta; *APOE*, apolipoprotein E; CI, confidence interval; LIBRA, Lifestyle for Brain Health score; PACC-3, three-test Preclinical Alzheimer's Cognitive Composite; WRAT3, Wide Range Achievement Test (3rd edition).

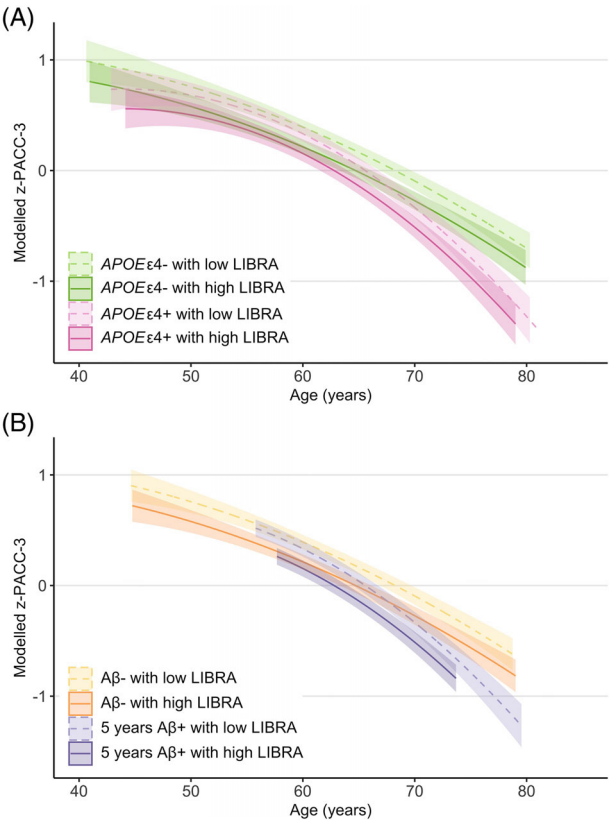

FIGURE 1 Associations of *APOE* ε4, Aβ duration, and LIBRA with longitudinal cognition. For visualization purposes, the modelled longitudinal z-PACC-3 trajectories from the final reduced model (Table 3) are depicted above for *APOE* ε4 non-carriers (*APOE* ε4−; green) and carriers (*APOE* ε4+; pink, panel A) and for baseline Aβ durations of −10 years (Aβ−; orange) and +5 years (Aβ+; purple, panel B) by low baseline LIBRA risk (dashed lines) and high baseline LIBRA risk groups (solid lines). Low and high LIBRA risk groups were created using the lower and upper LIBRA risk tertiles. The plots show the group-level modelled PACC-3 simple slopes (lines) and confidence intervals (shaded regions) over the range of ages present in each group. Panel A ($N = 1215$ subjects; years of cognitive follow-up, Mean (standard deviation [SD]) = 6.4 [3.5]) demonstrates that a healthy baseline lifestyle (e.g., low LIBRA tertile; dashed lines) was associated with better cognitive performance across *APOE* ε4 carriers and non-carriers, and *APOE* ε4 carriage (pink) was associated with faster PACC-3 decline. Panel B ($N = 285$ subjects; years of cognitive follow-up, Mean [SD] = 7.6 [3.0]) demonstrates that in the PiB imaging subset, lower baseline LIBRA risk (dashed lines) was associated with better overall PACC-3 performance across individuals with and without elevated Aβ, and longer Aβ duration (purple) was associated with faster PACC-3 decline. Aβ, amyloid beta; *APOE*, apolipoprotein E; CI, confidence interval; LIBRA, Lifestyle for Brain Health index; PACC-3, three-test Preclinical Alzheimer's Cognitive Composite; PiB, Pittsburgh compound B

significant LIBRA × Aβ duration × age interaction (LIBRA × Aβ duration × age^2, $P = .67$; LIBRA × Aβ duration × age, $P = .95$, Table S2 in supporting information). In the final reduced model in the PiB subset (Table 3, Figure 1B), baseline LIBRA was associated with better PACC-3 performance ($P < .001$) and both the linear and quadratic interactions between Aβ duration and age indicated significantly faster rates of PACC-3 decline among those who were Aβ positive longer. Results were similar when investigating the associations of concurrent LIBRA with *APOE* ε4 carriage and Aβ duration on PACC-3 decline (Tables S3–S4 in supporting information).

3.3 | LIBRA and Aβ burden

A secondary goal was to examine whether baseline LIBRA was associated with Aβ plaque accumulation. After adjusting for age at the most recent PiB visit, *APOE* ε4 carriage, and time between baseline

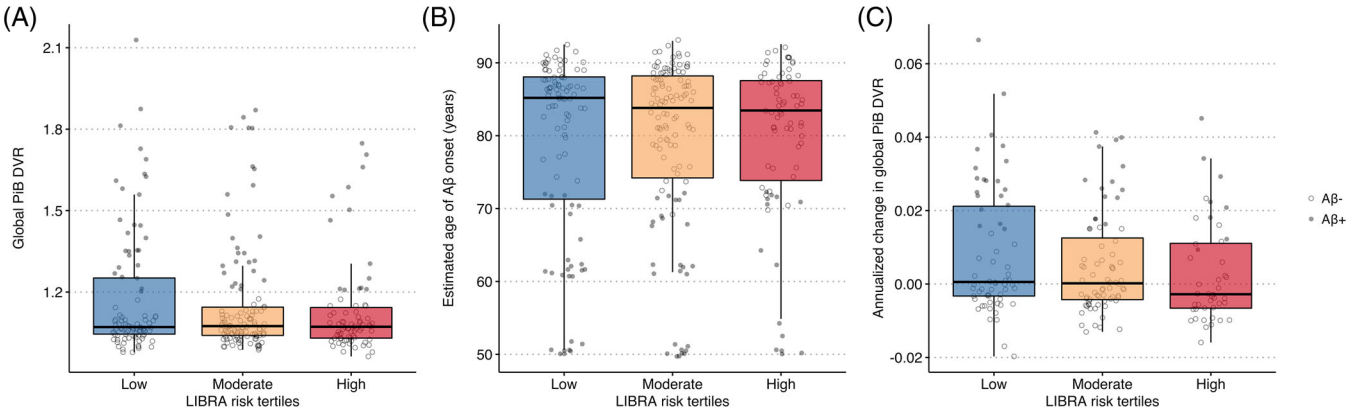

FIGURE 2 Comparisons of amyloid PET measures across LIBRA risk groups. Baseline lifestyle-based dementia risk was defined using baseline LIBRA risk groups. Low risk (blue) was defined as LIBRA between −4.2 and 0, moderate risk (yellow) was defined as LIBRA between 0.1 and 2.0, high risk (red) was defined as LIBRA between 2.1 and 8.1. Aβ positivity (+/−; shaded circles) was defined as global PiB DVR > 1.19. A and B, Global PiB DVR and estimated age of Aβ onset for low-, moderate-, and high-risk LIBRA groups, respectively ($N = 285$). C, Change in global PiB DVR per year for low-, moderate-, and high-risk LIBRA groups with more than one Aβ PiB PET scan ($N = 178$; years of PiB follow-up, Mean [standard deviation] = 6.4 [2.3]). No significant differences between baseline LIBRA risk groups with Aβ PET measures were observed (Table 2). Aβ, amyloid beta; *APOE*, apolipoprotein E; DVR, distribution value ratio; LIBRA, Lifestyle for Brain Health index; PET, positron emission tomography; PiB, Pittsburgh compound B

LIBRA and PiB visit, there was no evidence for a cross-sectional association of baseline LIBRA with global PiB DVR ($N = 285$, β [standard error (SE)] = −0.01 [0.01], $P = .11$) or estimated age of Aβ onset (β [SE] = 0.23 [0.33], $P = .49$; Table S5 in supporting information). In the subset with multiple PiB scans ($N = 178$; years of PiB follow-up, Mean [standard deviation (SD)] = 6.4 [2.3]), there was no significant association between LIBRA and the annualized change in global PiB burden (β [SE] = −0.0003 [0.0006], $P = .54$; Table S5). Results were similar when investigating the associations of Aβ PET measures across LIBRA tertiles (Figure 2, Table 2).

4 | DISCUSSION

This longitudinal study investigated the association of health and lifestyle, quantified using a multivariable lifestyle-based dementia risk score (LIBRA), with cognitive trajectories and AD pathophysiology in initially cognitively unimpaired, late-middle aged adults enriched for risk of AD. Baseline LIBRA scores, reflecting a brain-healthy late-midlife lifestyle, were associated with better overall cognitive performance, but not the rate of cognitive decline or the accumulation of Aβ plaques. Additionally, baseline LIBRA did not moderate the negative associations of *APOE* ε4 carriage or Aβ duration with longitudinal cognitive decline over the duration of the study. Collectively, these findings suggest that a healthy lifestyle in late-midlife is important for overall cognition, but may not influence Aβ accumulation or attenuate *APOE* ε4 or Aβ-related cognitive decline in those unimpaired at baseline.

These results are in line with previous population and patient-based cohort studies showing that LIBRA scores are related to cognitive functioning, but not the individual course of cognitive decline.[17,18,32] In our AD risk–enriched sample, there was no evidence for synergy between LIBRA and *APOE* ε4 carriage (LIBRA × *APOE* ε4 carriage × age was not significant [NS]). These findings add to a previous study of LIBRA, demonstrating no significant interactions between midlife LIBRA and *APOE* ε4 carriage on risk of MCI or dementia,[15] and suggest that LIBRA in late-midlife does not moderate *APOE* ε4-related cognitive decline in the early pre-symptomatic phase of AD. Additionally, we found no evidence for synergy between LIBRA and Aβ duration (LIBRA × Aβ duration × age was NS) on longitudinal cognitive decline. These results align with recent studies suggesting that lifestyle and cardiovascular risk factors embodied by LIBRA may generally increase risk for cognitive impairment and dementia, but are not specific to AD.[33–37] Notably, when accounting for the negative influence of *APOE* ε4 and Aβ duration on cognitive decline, baseline LIBRA remained strongly associated with better overall cognitive performance. Supplemental analyses examining concurrent lifestyle revealed similar results. Together, these findings suggest that health and lifestyle are important for general cognition throughout mid- and late-life, but may not impact early AD-related cognitive trajectories.

In WRAP, we did not observe a clear association between baseline LIBRA and Aβ burden; analyses failed to show an association between markers of early Aβ development and lifestyle in late-midlife. These findings are consistent with several studies among cognitively unimpaired individuals that did not find a correlation between vascular health and Aβ burden.[38–40] For example, the largest study to date of preclinical AD involving cognitively healthy people with Aβ imaging showed that elevated brain Aβ was associated with *APOE* ε4 carriage but not with multiple self-reported lifestyle risk factors encompassed by the LIBRA score (e.g., physical activity, body mass index, alcohol intake, smoking).[37] Our results, showing a lack of an association between LIBRA and brain Aβ among cognitively normal

late-middle aged adults, in combination with a recent cross-sectional population-based study showing an association of LIBRA with non-AD specific measures of brain health (e.g., white matter hyperintensities and brain atrophy)[16] suggest that lifestyle, as indexed by LIBRA, may play an important role in general brain health, but may not influence early AD-related brain changes.

These results are best understood in the context of the study sample. With the relatively long period of follow-up and enrichment for AD risk, WRAP is uniquely powered to detect AD-related changes in late-midlife during the pre-symptomatic timeframe. Notably, in the current study, <5% of individuals progressed to clinical levels of impairment. Thus, studies with a greater proportion of individuals progressing to MCI or dementia will be needed to fully elucidate the moderating role of lifestyle on AD-related clinical progression in the symptomatic timeframe. Additionally, it is worth considering that given the preclinical timeframe (≈60 years of age at baseline) and limited sample with elevated Aβ, we may have been underpowered to detect an interaction between LIBRA and Aβ-related cognitive decline. As Aβ accumulates over years to decades, it will be important to continue to examine the associations between midlife lifestyle, Aβ accumulation, and cognition over longer periods of follow-up.

The comprehensive study visits in WRAP made it possible to operationalize LIBRA factors based on clinical data from physical examination in combination with self-reported medical history. While data on most LIBRA factors were available, the absence of diet, which is a protective LIBRA factor, could have weakened the overall LIBRA score. Also, it remains unknown whether or the extent to which pharmacological treatment of LIBRA factors may have influenced our findings. Additionally, participation requires serial cognitive and health assessments, which may have resulted in a sample consisting of individuals with better overall health and lifestyle, and consequently, those with a higher range of lifestyle-related dementia risk may be underrepresented in the study sample. Finally, it is worth noting that WRAP reflects the demographics (e.g., primarily White) and health characteristics (e.g., rates of obesity, hypertension, diabetes) of the Wisconsin population, which reduces the generalizability of our findings.[41] Larger, more representative samples will be necessary to understand the impact of lifestyle on AD-related cognitive changes in late-midlife.

5 | CONCLUSIONS

In this late-middle aged AD risk–enriched sample, lower LIBRA scores, indicating a brain-healthy lifestyle, were strongly associated with better overall cognitive performance when accounting for the negative influence of *APOE* ε4 and Aβ duration on preclinical cognitive decline. There was no evidence that LIBRA in late-midlife was related to Aβ accumulation or moderated *APOE* ε4 or Aβ-related cognitive decline. Lifestyle, as indexed by LIBRA, may not be related to pathophysiologic or cognitive changes in the early, preclinical stages of the AD continuum; whether lifestyle contributes to AD progression later in the disease trajectory warrants further study.

ACKNOWLEDGMENTS

This publication was supported by NIH R01AG027161 (Johnson), NIH RO1AG021155 (Johnson), AARF 19614533 (Betthauser), NICHD P50HD105353 (Qiang), and S10 OD025245-01 (Christian), and the University of Wisconsin Institute for Clinical and Translational Research NIH UL1TR002375 (Cody). We extend our deepest thanks to the WRAP participants and staff for their invaluable contributions to the study.

CONFLICTS OF INTEREST

Dr. Johnson has participated on an advisory panel for and received an equipment grant from Roche Diagnostics, and he has received support (sponsoring of an observational study and provision of precursor for tau imaging) from Cerveau Technologies. No other disclosures were reported. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Cody KA, Koscik RL, Erickson CM, et al. Associations of the Lifestyle for Brain Health index with longitudinal cognition and brain amyloid beta in clinically unimpaired older adults: Findings from the Wisconsin Registry for Alzheimer's Prevention. *Alzheimer's Dement*. 2022;14:e12351. https://doi.org/10.1002/dad2.12351